REMARKS

As noted above, this amendment is being filed with a Request for Continued Examination. Applicants also request an interview with the Examiner once the Examiner has reviewed the present amendment prior to issuance of an Action other than a Notice of Allowance.

Claims 41, 56, 61, 66, 75, 80, 81, 82, 87, 88, 89, 90, 91, 92, 93, 94, 95 and 96 have been amended. Support for the amendments to claims 41, 66, 80, 81, 82, 87, 89, 91, 93 and 95 can be found, for example, at paragraph [0099] and paragraph [0004] of U.S. Publication No. 2002/0127697 and Figure 2A. Support for the amendments to claims 56 and 75, can be found at paragraph [0075] of U.S. Publication No. 2002/0127697 and in the claims as originally filed. Support for the amendment to claim 61 can be found, for example, in Example 1, beginning at paragraph [0096] of U.S. Publication No. 2002/0127697. Support for the amendments to claims 88, 90, 92, 94 and 96 can be found for example, at paragraph [0090] of U.S. Publication No. 2002/0127697. New claims 97-121 have been added. Support for new claims 97-121 can be found in the claims as originally filed and throughout the specification including, for example, paragraph [0085] and paragraph [0062] of U.S. Publication No. 2002/0127697. No new matter is added by way of these amendments.

Claim Objection

37 C.F.R. 1.75(c) states that one or more claims may be presented in dependent form, referring back to and further limiting another claim or claims in the same application. There is nothing requiring that a claim, such as claim 51, depend from a previously numbered claim. 37 C.F.R. 1.75(c) only states that multiple dependent claims cannot serve as a basis for another multiple dependent claim. Furthermore, 37 C.F.R. 1.126 states that the Examiner will renumber the claims as appropriate once they are allowed. Applicants respectfully request withdrawal of this objection with the understanding that the Examiner will re-number and re-order the claims as necessary when the claims are allowed.

35 U.S.C. § 112, First Paragraph, Enablement

Claims 41-44, 49-51, 56, 58, 59, 61, 63-73, 75, 77-82 and 87-96 were rejected for allegedly lacking enablement for systemic administration of a retrovirus. This rejection is moot with regard to canceled claim 77. Applicants traverse this rejection as it may apply to the

amended claims and new claims. The Examiner concedes that the application is enabled for local or topical administration of a retrovirus. The legal requirement is not to prove enablement for each and every species that may fall within the scope of the claim. Applicants again point out that, as held by *Invitrogen Corp. v. Clontech Labs* and *Johns Hopkins Univ. v. CellPro, Inc.,* the enablement requirement is met if the description enables **any mode** of making and using the invention. *Invitrogen Corp. v. Clontech Labs.*, 429 F.3d 1052 (Fed. Cir. 2005); *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998). Thus, the standard of enablement has been met by the Applicants. However, the Examiner maintained this rejection based on the argument that the Applicant has only submitted data that the vectors of the claimed method are useful via intratumoral injection. However, in the Amendment and Response filed January 26, 2007, Applicants submitted data by one of the inventors of the present application, Dr. Kasahara, demonstrating that RCR vectors comprising the GFP marker gene delivered *via the bloodstream* selectively target tumor cells in the liver while sparing normal hepatocytes and without dissemination to extrahepatic normal tissues. (Hiraoka et al., *Clinical Cancer Research* 12:7108-16 (2006)). Also submitted in the Amendment and Response filed January 26, 2007 were data extracted from a manuscript recently submitted for publication showing that in the same mouse model RCR vectors comprising cytosine deaminase, a suicide gene, can selectively target tumor cells resulting in significant tumor inhibition. Furthermore, a declaration by Dr. Kasahara was submitted July 28, 2006, which described the manner in which one skilled in the art can make and use the methods defined by the claims based on the disclosure provided in the present application and the high level of skill in the art. Thus, Applicants have provided ample evidence that the claimed vectors are effective in the treatment of a cell proliferative disorder in a subject. Applicants respectfully request that the Examiner set forth why this previously submitted data do not address the Examiner's concerns. One of skill in the art would clearly be able to administer a retrovirus via many routes of administration. Therefore, the claims are enabled, and Applicants respectfully request withdrawal of this rejection.

35 U.S.C. § 103

Claims 41-45, 49-51, 56, 61, 66, 70, 71, 73, 75, 77-80, 87, 89 and 91 were rejected for allegedly being obvious based on Ram et al., Cancer Research 53:83-8 (1993) ("Ram") in view of Martuza, Nature Medicine 3:1323 (1997) ("Martuza") and U.S. Patent No. 5,585,096 ("the

'096 patent"). This rejection is moot with regard to canceled claim 77. Applicants traverse this rejection as it may apply to the amended claims and new claims.

The present claims are drawn to methods of treating cell proliferative disorders or glioblastomas by administering a replication competent oncoretrovirus to a subject. The claims have been amended to recite a cassette that includes an IRES sequence operably associated with a heterologous sequence. The cassette is positioned between the env termination codon and the beginning of the 3' LTR region. Applicants discovered that this combination of components is suitable for constructing an oncoretrovirus that: 1) efficiently transduces a high percentage of dividing mammalian cells with a transgene; 2) stably maintains the presence and expression of the transgene through multiple cell passages; and 3) selectively infects only those cells undergoing cell division, such as cells associated with a cell proliferative disorder. The combination of transduction efficiency, transgene stability, and target selectivity was unknown in any recombinant replication competent mammalian oncoretrovirus prior to the instant vector. The vectors used in the claimed methods alleviate problems associated with insert instability while maintaining the transcriptional activity of the transgene and the translational viability of the encoded polypeptide. When placed in a mammalian oncoretroviral background the cassette is useful for the stable expression of a transgene coding sequences including marker genes such as green fluorescent protein (GFP), suicide genes such as thymidine kinase, cytosine deaminase (CD) or purine nucleoside phosphorylase (PNP), and genes encoding cytokines such as interferon.

The cited portions of Ram describe a method that utilizes "retroviral producer cells" injected at the site of a tumor (see page 86, column 2, last paragraph of Ram). The producer cells support the *in situ* production of a retroviral vector containing a suicide gene. The producer cells are necessary because the vector is *not* replication competent. Further, the nucleic acid sequence encoding the suicide gene is located "just downstream of the 5' long terminal repeat sequence" (see page 84, column 1, lines 2-4 of Ram). Therefore, the cited portions of Ram fail to describe a *replication competent* oncoretrovirus in the absence of a producer cell to achieve efficient transduction. The cited portions of Ram also fail to appreciate the desirability of positioning a nucleic acid sequence encoding a therapeutic polypeptide in a non-LTR region of the viral vector. The cited portions of Martuza and the '096 patent allegedly describe replication

competent viral vectors derived from adenovirus and herpes simplex virus. Nevertheless, both references fail to remedy the deficiencies of Ram because, like Ram, the cited portions of Martuza and the '096 patent fail to appreciate the importance of positioning a cassette that includes an IRES sequence operably associated with a heterologous sequence 5' to the 3' LTR and 3' to the envelope gene of the viral vector. Furthermore, absent the disclosure provided by the present application, one of skill in the art would not have known how to modify a retrovirus in order to make it replication competent. The claims are directed to retroviruses, which are RNA viruses. Martuza and the '096 patent describes adenoviruses and herpesviruses, which are DNA viruses. Therefore, one of skill in the art would not have known how to make an RNA virus replication competent based on a disclosure of how to make a DNA virus replication competent as their genomes are completely different. Thus, the cited portions of Martuza and the '096 patent cannot make up for the deficiencies of Ram.

Not only do the cited references fail to identify predictable solutions for achieving a replication competent oncoretrovirus capable of delivering a therapeutic polypeptide to dividing cells, they also fail to provide all the components necessary for the production of the vector set forth in the claimed methods. In contrast, Applicants have succeeded in designing a replication competent oncoretroviral vector with an enhanced capability to stably deliver a heterologous sequence to a dividing cell. Once integrated into a target cell, the vector produces a therapeutic polypeptide encoded by the heterologous sequence. In addition, viral particles which infect neighboring dividing cells are also produced.

The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1731 (2007). Applicants submit that in cases involving methods of treatment utilizing replication competent retroviruses, it remains necessary to identify some reason that would have led the skilled artisan to combine known retroviral components in a particular manner, and in a particular sequence, to establish a *prima facie* case of obviousness. Here, Ram selected a system

that utilized "producer cells" to produce viral vectors *in situ*. Significantly, the cited portions of Ram fail to describe how to accomplish production of the vector in the absence of producer cells. The cited portions of Ram also fail to describe positioning a heterologous nucleic acid sequence in the viral genome so that it is efficiently expressed and remains stable during viral replication. The cited portions of Martuza and the '096 patent fail to remedy the deficiencies of Ram because they are silent with regard to the positioning of the heterologous sequence. Accordingly, the cited portions of Ram, Martuza and the '096 patent, in combination, fail to describe utilizing a replication competent oncoretrovirus as described in the present application in a manner that achieves the claimed methods. More specifically, the cited portions of Ram, Martuza and the '096 patent, in combination, fail to provide a reasonable expectation that the combination of viral components would result in a replication competent oncoretrovirus useful for treating cell proliferative disorders. Therefore, the claims are not obvious based on Ram, Martuza and the '096 patent, and Applicants respectfully request withdrawal of this rejection.

Claims 41-45, 49-51, 56, 58, 59, 61, 66, 70, 71, 73, 75, 77-80 and 87-92 were rejected for allegedly being obvious over Ram in view of Martuza and the '096 patent and further in view of Kuryama et al., *Int. J. Cancer* 71:470-5 (1997) ("Kuryama") and Yan et al., *Prostate* 32:129-39 (1997) ("Yan"). As discussed above, Ram, Martuza and the'096 patent, in combination, fail to disclose or suggest each and every element of the claims or provide one of skill in the art with a reasonable expectation of success. The cited portions of Kuryama and Yan fail to make up for these deficiencies. Kuryama was cited for describing thymidine kinase (tk) under control of a liver-specific albumin promoter. Yan was cited for describing a probasin promoter. Therefore, the cited portions of Ram, Martuza, the '096 patent, Kuryama and Yan, in combination, do not disclose or suggest a replication competent oncoretrovirus comprising a cassette that includes an IRES sequence operably associated with a heterologous sequence positioned between the env termination codon and the beginning of the 3' LTR region. Specifically, the cited portions of Kuryama and Yan fail to make up for the deficiencies of Ram, Martuza and the '096 patent since they fail to describe the importance of the positioning of the cassette. Thus, the cited portions of Ram, Martuza, the '096 patent, Kuryama and Yan, in combination, fail to describe utilizing a replication competent oncoretrovirus as described in the present application in a manner that achieves the claimed methods. Therefore, the claims are not obvious based on Ram, Martuza,

the '096 patent, Kuryama and Yan, and Applicants respectfully request withdrawal of this rejection.

Claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 77-80, 81, 82, 87, 89-91, 93 and 95 were rejected for allegedly being obvious over Ram in view of Martuza and the '096 patent and further in view of Kasahara et al., *Science* 266:1373-6 (1994) ("Kasahara"). The cited portions of Kasahara fail to make up for the deficiencies of Ram, Martuza and the '096 patent. Kasahara was cited by the Examiner for describing a replication incompetent retroviral vector encoding a chimeric envelope protein. Therefore, the cited portions of Ram, Martuza, the '096 patent, and Kasahara, in combination, do not disclose or suggest a replication competent oncoretrovirus comprising a cassette that includes an IRES sequence operably associated with a heterologous sequence positioned between the env termination codon and the beginning of the 3' LTR region. Specifically, the cited portions of Kasahara fail to describe the importance of the positioning of the cassette. Thus, the cited portions of Ram, Martuza, the '096 patent, and Kasahara, in combination, fail to describe utilizing a replication competent oncoretrovirus as described in the present application in a manner that achieves the claimed methods. Therefore, the claims are not obvious based on Ram, Martuza, the '096 patent, and Kasahara, and Applicants respectfully request withdrawal of this rejection.

Claims 41-45, 49-51, 56, 61, 63-70, 71-73, 75, 77-80, 81, 82, 87, 89-91 and 93-96 were rejected for allegedly being obvious over Ram in view of Martuza and the '096 patent and further in view of Kasahara and Kuryama. The combination of Ram, Martuza, the '096 patent, Kasahara and Kuryama fails to describe each and every element of the claims or to provide one of skill in the art with a reasonable expectation of success. The cited portions of Ram, Martuza, the '096 patent, Kasahara and Kuryama, in combination, do not disclose or suggest a replication competent oncoretrovirus comprising a cassette that includes an IRES sequence operably associated with a heterologous sequence positioned between the env termination codon and the beginning of the 3' LTR region. Thus, the cited portions of Ram, Martuza, the '096 patent, Kasahara and Kuryama, in combination, fail to describe utilizing a replication competent oncoretrovirus as described in the present application in a manner that achieves the claimed methods. Therefore, the claims are not obvious based on Ram, Martuza, the '096 patent, Kasahara and Kuryama, and Applicants respectfully request withdrawal of this rejection.

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Respectfully submitted,

Date: October 31, 2007

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